REMARKS

Claims 28-51 are pending. Claims 30-41, 44-48 and 51 are withdrawn from further consideration by the Examiner under 37 CFR 1.142(b), as being drawn to a non-elected inventions. Claims 28, 29, 42, 43, 49 and 50 have been rejected on various grounds. In this response, applicants amend claims 28, 29, 42, 43, 49 and 50 and provide arguments against the remaining rejections. Reconsideration and allowance are requested.

Claim Objections

The Examiner has objected to claim 42 for a typographical error. In response, Applicants amend the claim appropriately.

Definiteness Rejections

The Examiner rejects claims 28, 29, 42, 43, 49 and 50 on pages 3-5 of the Office Action on indefiniteness grounds.

For definiteness, a claim need only reasonably apprise those skilled in the art of the utilization and scope of the invention. *Hybritech, Inc. v. Monoclonal Antibodies,* 231 USPQ 81, 94-95 (1986). Words are to be given their plain meaning as understood by the person of ordinary skill in the art, particularly given the limitations of the English language. *See* MPEP §§ 707.07(g); 2111.01 (Rev. 1, February 2000). Claims are to be given their broadest reasonable interpretation consistent with applicants' specification. *See* MPEP § 2111 (Rev. 1, February 2000). In sum, in order to reject the claims on definiteness grounds, it is incumbent on the examiner to show how and why the skilled person having applicants' specification would not be apprised of the invention by the language-at-issue. The rejections are discussed below.

a) The Examiner asserts that the phrase "as the only structurally and functionally intact SCR domains of CR1" "is confusing". The Examiner also opines that "it is unclear what relationship CR1 has to the claimed polypeptide". In response,

Applicants respectfully disagree with the Examiner and point out that there are only 30 short consensus repeats (SCR) in CR1 and was well known in the art at the time the application was filed (See, for example, page 691, paragraph 1, lines 2-4 and page 693, right column, last paragraph, in Birmingham *et al.* J. Immunol. 153(2):691-700)(1994)) (enclosed). Applicants further explain that the phrase "as the only structurally and functionally intact SCR domains of CR1" means that the polypeptide comprises one to four SCRs, and that these SCRs are structurally and functionally similar to these in the native wild type protein (See, for example, Figure 10, page 699, in Birmingham *et al.* J. Immunol. 153(2):691-700)(1994)) (enclosed). Again, the Applicants point out how to measure the function of these polypeptides in Example 11 of the application (page 38 of the published WO98/39433 PCT specification). Furthermore, the term "SCR" is well known in the art that such skilled artisan would understand "what is and what is not an SCR".

b) The Examiner objects to the phrase "wherein at least one of the native amino acids is substituted" in one or more of the above mentioned claims. In response, Applicants point out that the "native amino acids" refer to the SCRs comprising the polypeptide as described in the claim.

c) On page 4 of the Office Action, the Examiner states that the "positions of the proposed amino acid substitutions are indefinite". In response, Applicants point out that the substitutions are in relation to the native CR1 sequence starting at SCR1, well known in the art, particularly given related patents from Mossakowska *et al.* (See, for example, US Patent No. 5,833,989)

d) The Examiner rejects claims 42, 43 and 49 for using the term "derivatives". In response the Applicants point out that the "derivatives" are the polypeptides comprising SCRs, well known in the art (See, for example, US Patent No. 5,833,989 and 5,859,223) and as set forth in SEQ ID NO: 1 with at least one of the listed substitutions.

e) The Examiner asserts that the claim 42 is indefinite for using the term "Low affinity". Applicants amend the claim 42 by incorporating the affinity dissociation constant range to the claim.

f) On page 5 of the Office Action, the Examiner objects to claims 42 and 49 on the grounds that the first lines of the claims are unclear. Applicants accordingly amend the claims. The new language of the amended claims thus more distinctly claims the desired subject matter.

g) The Examiner states that "[I]n claim 40 the term 'thermodynamic additivity' renders the claim indefinite". Since claim 40 has been withdrawn from consideration at this time and that it does not contain such a term, Applicants believe that the Examiner meant to refer to claim 42. In response, Applicants respectfully disagree with the Examiner and point out that the term has been well known to one skilled in the art and has been in practice (See, for example, page 699, paragraph 1, lines 1-4, in Murphy and Gill. J. Mol. Biol. 222(3):699-709 (1991)).

h) Applicants amend the claims 28 and 42 following the Examiner's suggestion.

j) Applicants amend claims 28, 42, 49, and 50 where applicable, per Examiner's suggestion.

Written Description Rejections

On page 5 of the Office Action, the Examiner rejected claim 43 for written description of polypeptide derivatives. The Examiner alleges that "the specification discloses a polypeptide of SEQ ID NO: 1, yet the claim encompasses polypeptide derivatives not described in the specification".

The USPTO issued its final guidelines for written description (66 Fed. Reg. 1099) early this year. The written description guidelines first instruct examiners to determine what the claim as a whole covers and then review the entire specification to determine whether all subject matter that is essential to the invention is actually recited in the

claims. See written description guidelines at II(A)(1), (2). Next, the examiners are instructed to determine whether the applicant was in possession of all that is claimed. See the written description guidelines at II(A)(3). According to the guidelines, possession of a claimed invention can be shown by disclosure of structural characteristics, functional characteristics that correlate with structure or combinations thereof. See the written description guidelines at II(A)(3)(a). Claims that encompass a genus must be supported by a written description of a representative number of species. See the written description guidelines at II(A)(3)(a)(2). The written description of the representative species of the genus can be shown by disclosure of structural characteristics, functional characteristics that correlate with structure or combinations thereof. Applicants submit that the examiner has not satisfied these guidelines in making the rejection, which alone is grounds for withdrawal of the rejection.

Nevertheless, Applicants herein demonstrate that the structural requirements set forth in claim 43 find correspondence in the specification. Applicants submit that it is clear that they had possession of the subject matter claimed in claim 43. Given the correspondence and applicants' identification of this correspondence, a heavy burden is placed upon the examiner to reject the claims. *See* MPEP § 2163.04 (Rev. 1, February 2000). For example, applicants point out that the specification describes additional derivatives of membrane binding sequences, in addition to SEQ ID NO: 1, on page 10 of the specification. The specification also cites reference (See, for example, Blackshear. J. Biol. Chem. 268:1501-1504 (1993)) to sources where further examples of suitable membrane binding elements and amino acids sequences could be found (see page 10).

Thus, withdrawal of the written description rejection is solicited.

Obviousness Rejections

On page 7-8 of the Office Action, the Examiner has rejected claims 28, 29, 42, and 50 as obvious over US Patent No. 5,545,619 in combination with Hourcade *et al.*, J. Biol. Chem. 265(2):974-980 (1990). The Examiner alleges that "U.S. Patent No:

5,545,619 teaches a soluble polypeptide (CR1) comprising one to four short consensus repeats [SCR] of the long homologous repeat A (LHR-A) and related polypeptides termed RCA polypeptide (see col 6), methods of producing mutations in said polypeptides (see col 7)".

At the outset, applicants note the examiner must show all of the recited claim elements in the combination of references that make up the rejection. When combining references to make out a *prima facie* case of obviousness, the examiner is obliged to show by citation to specific evidence in the cited references that (i) there was a suggestion to make the combination and (ii) there was a reasonable expectation that the combination would succeed. Both the suggestion and reasonable expectation must be found within the prior art, and not be gleaned from applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988); *see also* MPEP §§ 2142-43 (Rev. 1, February 2000).

When an examiner alleges a *prima facie* case of obviousness, such an allegation can be overcome by showing that (i) there are elements not contained in the references or within the general skill in the art, (ii) the combination is improper (for example, there is a teaching away or no reasonable expectation of success) and/or (iii) objective indicia of patentability exist (for example, unexpected results). *See U.S. v. Adams*, 383 U.S. 39, 51-52 (1966); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve*, 230 USPQ 416, 419-20 (Fed. Cir. 1986).

Applicants respectfully traverse the rejections and point out at the time of the filing of instant application CR1 and its SCR components were known to skilled artisan and the present invention is relevant to non-obvious mutations made in CR1 including "SCR3," which is not in the teachings of US Patent No. 5,545,619 nor Hourcade et al. The US Patent No. 5,545,619 in combination with Hourcade et al. concerns CR1 diversity rather than purposeful mutation and substitutions as disclosed in the instant application. At the time of the invention, SCR3 was known as an active polypeptide fragment and it was not obvious to skilled artisan that mutations made in SCR3 would

not render the polypeptide inactive. It was believe at the time of invention that such mutations/substitutions would result into an inactive polypeptide.

The Examiner further refers to "mutations disclosed by Hourcade *et al.*, (see Figure 3), [and] as pointed to by U.S. Patent No: 5545619" and alleges that "amino acid sequences having mutations recited in the instant claims are encompassed by the invention (see col. 6, lines 6-15)". Applicants respectfully disagree with the Examiner's interpretation of the prior art U.S. Patent No: 5,545,619 and notes as above that the prior art does not teach mutation. Applicants points out that Hourcade *et al.* describes natural substitutions in CR1, which does not describe or provide indication to any of the purposeful substitutions in SCR3 as described in the instant application and recited in the claims. Applicants further point out that Hourcade *et al.* discloses diversity between the wild-type CR1 amino acids sequence and the CR1-like predicted sequences. There are 39 CR1-like predicted sequences (As shown on Figure 3), but Hourcade *et al.* do not teach which one is compatible with retention of activity in multi-SCR constructs; none of which were expressed or assayed in prior to the filing of this application. In fact, prior to the current invention, no domain of the CR1-like gene was expressed and studied. Therefore, it would not have been obvious to design a construct such as CM7 (SEQ ID NO: 1). Thus, at the time the invention was made, there would have been no "reasonable expectation of success," to produce polypeptides of current invention "having the amino acid sequence taught by Hourcade et al. when practicing the invention disclosed in the U.S. Patent No: 5,545,619."

In response to the Examiner's statement on page 8 on "RCA proteins" and reference to Hourcade et al.'s "col. 6, lines 6-15", and "the last paragraph of col. 8" the Applicants further refers to the arguments made above and point out that the referred citations do not teach polypeptides of the current invention encompassing mutations/substitutions in CR1 SCR3 domain.

Applicants therefore submit that the Examiner has not established a *Prima facie* case of obviousness, and therefore respectfully request withdrawal of the rejection.

On page 8-9 of the Office Action, the Examiner rejected claims 43 and 49 allegedly as being unpatentable over US Patent No. 5,545,619 in view of Hourcade et al., J. Biol. Chem. 265(2):974-980, 1990, as applied to claims 28, 29, 42 and 50 and in further view of Clissold et al., Eur. J. Immunol. 23:2346-2352, 1993. and U.S. Patent No: 5,936,092. The Examiners asserts that "Clissold et al. teach that the addition of a membrane binding element to soluble CR1 increases the effectiveness of CR1". In response, the Applicants traverse the rejections and refer to arguments made in preceding paragraphs. Applicants further point out, at the time the invention was made, it was unpredictable and non-obvious to obtain an active polypeptide as a result of such mutations in SCR3. Thus, there would be no motivation to add membrane binding elements, based on the teaching of Clissold et al., to the SCR elements to increase the effectiveness. The mutation of the SCR3, as it was believed, would result into an inactive molecule, therefore the addition of the membrane binding elements would not increase the effectiveness of an inactive polypeptide. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing remarks and amendments, reconsideration of the application and allowance of the claims are requested. If any issues remain which the Examiner believes could be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at 202-912-2777.

Respectfully submitted,

August 24, 2001
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MARKED UP COPY OF AMENDED CLAIMS

28. (Once Amended) A soluble polypeptide comprising in sequence one to four short consensus repeats (SCR) of long homologous repeat A (LHR-A) selected from the group consisting of SCR 1, 2, 3, and 4 [of long homologous repeats A (LHR-A)] as the only structurally and functionally intact SCR domains of CR1 and including at least SCR3, wherein at least one of the native amino acids are substituted, wherein the substitutions are selected from the group consisting of Val at position 4, Asp at position 19, Ser at position 53, Lys at position 57, Ala at position 74, Asp at position 79, Arg at position 84, Pro at position 91, Asn at position 109, Lys at position 116, Val at position 119, Ala at position 132, Thr at position 137, Ile at position 139, Ser at position 140, Tyr at position 143, His at position 153, Leu at position 156, Arg at position 159, Lys at position 161, Lys at position 177, Gly at position 230, Ser at position 235, and His at position 236.

29. (Once Amended) The soluble polypeptide according to claim 28 that comprises SCR selected from the group consisting of SCR 1, 2, 3, and 4 of LHR-A or SCR 1, 2 and 3 of LHR-A as the only structurally and functionally intact SCR domains of CR1.

42. (Once Amended) A soluble derivative of a soluble polypeptide [that comprises in sequence], wherein said soluble derivative comprises in sequence one to four short consensus repeats (SCR) of long homologous repeat A (LHR-A) selected from the group consisting of SCR 1, 2, 3, and 4 [of long homologous repeats A (LHR-A)] as the only structurally and functionally intact SCR domains of CR1 and including at least SCR3, wherein at least one of the native amino acids are substituted, wherein the substitutions are selected from the group consisting of Val at position 4, Asp at position 19, Ser at position 53, Lys at position 57, Ala at position 74, Asp at position 79, Arg at position 84, Pro at position 91, Asn at position 109, Lys at position 116, Val at position 119, Ala at position 132, Thr at position 137, Ile at position 139, Ser at position 140, Tyr at position 143, His at position 153, Leu at position 156, Arg at position 159, Lys at

position 161, Lys at position 177, Gly at position 230, Ser at position 235, His at position 236,

wherein [the derivative] said soluble polypeptide comprises at least two heterologous membrane binding elements with low membrane affinity, covalently associated with the polypeptide, wherein the elements are capable of interacting independently and with thermodynamic additivity with components of cellular membranes exposed to extracellular fluids,

wherein the membrane binding elements have an affinity with a dissociation constant of between at least about 1μM and 1mM.

43. (Once Amended) The [derivative] soluble polypeptide according to claim 42, comprising two to eight membrane binding elements selected from the group consisting of fatty acid derivatives, ligands of internal membrane proteins, sequences derived from the complementarity-determining region of monoclonal antibodies raised against epitopes of membrane proteins, and membrane binding sequences identified through screening of random chemical libraries.

49. (Once Amended) A process for preparing a soluble derivative of a soluble polypeptide [that comprises in sequence], wherein said soluble derivative comprises in sequence one to four short consensus repeats (SCR) of long homologous repeat A (LHR-A) selected from the group consisting of SCR 1, 2, 3, and 4 [of long homologous repeats A (LHR-A)]as the only structurally and functionally intact SCR domains of CR1 and including at least SCR3, wherein at least one of the native amino acids are substituted, wherein the substitutions are selected from the group consisting of Val at position 4, Asp at position 19, Ser at position 53, Lys at position 57, Ala at position 74, Asp at position 79, Arg at position 84, Pro at position 91, Asn at position 109, Lys at position 116, Val at position 119, Ala at position 132, Thr at position 137, Ile at position 139, Ser at position 140, Tyr at position 143, His at position 153, Leu at position 156, Arg at position 159, Lys at position 161, Lys at position 177, Gly at position 230, Ser at position 235, His at position 236, comprising

expressing DNA encoding the polypeptide portion of said derivative in a recombinant host cell and recovering the product and thereafter post translationally modifying the polypeptide to chemically introduce membrance binding elements.

50. (Once Amended) A pharmaceutical composition comprising (A) a therapeutically effective amount of a soluble polypeptide comprising in sequence one to four short consensus repeats (SCR) of long homologous repeat A (LHR-A) selected from the group consisting of SCR 1, 2, 3, and 4 [of long homologous repeats A (LHR-A)] as the only structurally and functionally intact SCR domains of CR1 and including at least SCR3, wherein at least one of the native amino acids are substituted, wherein the substitutions are selected from the group consisting of Val at position 4, Asp at position 19, Ser at position 53, Lys at position 57, Ala at position 74, Asp at position 79, Arg at position 84, Pro at position 91, Asn at position 109, Lys at position 116, Val at position 119, Ala at position 132, Thr at position 137, Ile at position 139, Ser at position 140, Tyr at position 143, His at position 153, Leu at position 156, Arg at position 159, Lys at position 161, Lys at position 177, Gly at position 230, Ser at position 235, and His at position 236, and (B) a pharmaceutically acceptable carrier or excipient.